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# PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| CRP-165PC | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US98/10909 | 29/05/1998 | 30/05/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>G01N33/50 | | |
| Applicant<br>CREATIVE BIOMOLECULES, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 17/12/1998 | 26.06.99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0 Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br>Montron , M<br>Telephone No. (+49-89) 2399 8711 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/10909

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-65 as originally filed

**Claims, No.:**

1-122 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-56,76-103.

because:

☒ the said international application, or the said claims Nos. 1-56,76-103 with respect to I.A. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-122 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-122 |
| Industrial applicability (IA) | Yes: | Claims | 57-75, 104-122 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**s s parat she t**

**VII. C rtain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

Item III:

Claims 1 to 56 and 76 to 103 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(i) PCT).

Item V:

1. WO-A-9403200 (document D1) discloses morphogen induced nerve regeneration and repair of damaged neurons, neural pathways and retina (see abstract and page 9, line 8; page 12, l. 13). In addition, compositions are disclosed consisting of biodegradable carriers which are locally or systemically administered, including orally, intravenously or parenterally (see page 10, l. 18 and page 13, l. 14; page 14, l. 33; page 17, l. 31). The morphogens are either administered alone or with compounds which enhance the solubility of the proteins or analogs (page 18, l. 5, page 20, l. 9). The following examples of morphogens are given: OP-1, OP-2, GDF-1, DPP, Vgl, Vgr-1, 60A and different BMPs (see page 18, line 23 to page 23, line 6). The biological functions of said morphogens were defined as follows: stimulate proliferation or differentiation of progenitor or differentiated cells, support growth and maintenance of differentiated cells (see page 27, l. 4). In addition, generic sequences of said morphogens are disclosed (see page 27, l. 26 to page 31, l. 37) and the C-terminal 96 to 102 amino acids of said proteins which have at least 70% homology to OP-1 (page 39, l.19). Thus, D1 is considered to be detrimental to the novelty of the subject-matter of claims 1 to 75.

   WO-A-9403600 (document D2) discloses soluble complexes of morphogenic proteins and compositions thereof (see abstract and page 1, l. 6). The morphogens of D2 are able to induce endochondral bone formation and are either locally or systemically administered (see page 1, line 21 to 25). In addition, a diagnostic method is disclosed for monitoring the concentration of said morphogens (page 3, l. 13). OP-1 from human or mouse origin and analogs thereof are disclosed as examples (page 5, l. 13). The morphogens could be used for the treatment of damages of bones, dentin, periodontal, liver, heart, nerve tissue and kidney or pancreas tissue (see page 9, l. 7 to 28 and page 51, l. 15). The composition is administered either orally, parenterally

or systemically (page 51, l. 27). The OP-1 is provided in an aqueous solution or together with a biodegradable matrix (page 52, l. 4 to page 53, l. 1). The doses administered vary from 10 ng/kg to 1 g/kg up to 0.1 µg/kg to 100 mg/kg (see page 57, l. 20). Consequently, D2 is considered to be detrimental to the novelty of the subject-matter of claims 29 to 122.

WO-A-9630038 (document D3) discloses peptide growth factors or analogs or fragments thereof having epidermal inducing activity which could be used as a pharmaceutical composition for wound healing, skin culture or the treatment of certain neural tumours (see abstract and page 27, line 30 to page 28, line 5 and page 33, line 4). BMP-4 is disclosed as an example (see page 10, l. 24). Thus, D3 is considered to be detrimental to the novelty of the subject-matter of claims 29 to 75.

US-A-5169837 (document D4) discloses purified novel water-soluble osteogenic factors for the induction of bone growth and pharmaceutical compositions thereof (see abstract, col. 3, line 22; col. 7, l. 1 to col. 8, l. 31). Moreover, bioassays for evaluating the morphogenic activity of said proteins or for the evaluation of a protein-dose dependent relationship are disclosed (col. 10, l. 22 and fig. 2). Thus, D4 is considered to be detrimental to the novelty of the subject-matter of claims 1 to 5, 8 to 12, 15, 20 to 22, 76 to 87, 90, 95 to 97, 104 to 109, 111 and 114 to 116.

EP-A-0714665 (document D5) discloses osteogenic proteins and a device for the induction of bone growth (abstract). OP-1 and CBMP IIa, CBMP IIb and CBMP III as morphogens are mentioned (page 4). A composition of said proteins is used to correct skeletal or dental abnormalities, to induce endochondral bone formation and cartilage repair (see page 5, line 27 to 49). Moreover, an in vivo method is disclosed for evaluating bone inducing activity of said proteins (page 25, line 20). Thus, D5 is considered to be detrimental to the novelty of the subject-matter of claims 1, 3, 5, 7 to 11, 15, 23 to 26, 28, 29, 35 to 40, 43, 49 to 54, 56, 57, 59, 62, 64, 68, 70 to 73, 75, 76, 80 to 87, 90, 96 to 101, 103, 104, 106, 109, 111, 115 to 120 and 122.

EP-A-0723031 (document D6) discloses biosynthetic water-soluble osteogenic proteins and devices containing them. Moreover, a pharmaceutical composition and methods for the induction of endochondral bone growth, treatment of dental abnormalities and cartilage repair in mammals are disclosed (see abstract and claims

10 and 18). Several "natural" and "synthetic" morphogens are mentioned (see page 6 to page 7, line 48). In addition, an in vivo rat bioassay is disclosed for the evaluation of the morphogenic activity of proteins (page 18, l. 6). The concentration of the morphogen administered is 25 mg (page 18, l. 20). Consequently, D6 is considered to be detrimental to the novelty of the subject-matter of claims 1, 5, 7 to 12, 15, 21 to 26, 28, 29, 35 to 40, 43, 49 to 54, 56 to 58, 61, 62, 64, 65, 68 to 73, 75, 76, 80 to 87, 90, 96 to 101, 103, 104, 106, 108, 109, 111, 112, 115 to 120 and 122.

WO-A-9305172 (document D7) discloses a screening method for compounds which can modulate the level of morphogenic proteins in a mammalian system (see abstract and page 4, l. 3 to page 5, l. 7). The assay disclosed is identical to the one used in the present application in order to find and evaluate said compounds. The only difference is that it refers particularly to substances which are able to modulate the level of a known morphogen, such as OP-1.

WO-A-9514104 (document D8) discloses a further in vivo method for identifying substances capable of inducing bone formation. However, like in D7, it is not the morphogen itself which is evaluated for being morphogenic but rather a substance which either stimulates or inhibits OP-1 gene expression (see abstract; page 4, line 12 to 26 and page 19, line 7).

Consequently, the subject-matter of claims 1 to 122 of the present application is not considered to be novel over the cited prior art. Thus, said claims do not fulfil the requirements of Article 33(2) PCT.

2. For the assessment of the present claims 1 to 56 and 76 to 103 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI:

The documents WO-A-9813509 filed at the 24.09.1997, published at 02.04.1998 and claiming the priority of 24.09.1996, US-A-5641743 filed at the 26.05.1995, published at 24.06.1997 and claiming the priority of 26.05.1995 and WO-A-9732033 filed at the 28.02.1997, published at 04.09.1997 and claiming the priority of 28.02.1996 could be relevant to the subject-matter of the present application if the priority of the claims is not valid. In addition, said documents could be relevant for the question of novelty under Article 54(3) and (4) EPC if the application enters the regional phase in Europe.

Item VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3, D4, D5 and D6 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

1. The terms:
"aged" used in claims 8, 22, 50, 97
"reduced capacity" used in claims 9, 11, 37, 39, 84, 86
"obese" used in claims 22, 50, 97
"hypertensive" used in claims 22
"steroidal drug user" used in claims 21, 49, 96
have a relative meaning and are thus vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

2. The term "defines a volume" used in claim 81 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

3. The subject-matter of claim 24 is already covered by the subject-matter of claim 23 rendering the scope of protection of said claim unclear, contrary to the requirements of Article 6 PCT. The same applies to the subject-matter of claims 52 and 51, 71 and 70, 99 and 98 and 118 and 117.

4. The subject-matter of claims 1, 3, 29, 31, 32, 57, 76, 78, 79 and 104 is vague and unclear since they are formulated in a "result to be achieved" manner without disclosing any substantial technical features. This renders the definition of the subject-matter of said claims and their scope unclear (Article 6 PCT).

5. There is no experimental support given in the application as filed that every "morphogen" sharing at least 70 % homology within the C-terminal 102-106 amino acids of the human OP1 protein does indeed induce tissue formation, tissue repair or enhances callus formation as claimed in claims 25, 53, 72, 100 or 119, contrary to the requirements of Article 6 PCT. Furthermore, the subject-matter of said claims is not disclosed by the description in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 5 PCT).

6. The same applies to the generic sequences as referred to in claims 28, 56, 75, 103 and 122 being disclosed on page 25, line 20 et seq. of the description in an uncountable number of different amino acid combinations. No biologic function has been disclosed for said alleged morphogenic proteins and due to an endless number of all possible combinations it is as well doubted that every combination has morphogenic properties. Moreover, for the skilled person it is not possible to find the potentially effective combinations in the claimed range of "generic" morphogenic proteins. Thus, the subject-matter of said claims is not disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 5 PCT).

# PATENT COOPERATION TREATY





From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

To:

CAMACHO, Jennifer A.
Testa,Hurwitz & Thibeault, LLP
High Street Tower
125 High Street
Boston, MA 02110
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 26.08.99 |
| Applicant's or agent's file reference | IMPORTANT NOTIFICATION |
| ~~CRP-165PC~~ 00960-510/WO | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US98/10909 | 29/05/1998 | 30/05/1997 |

Applicant
CREATIVE BIOMOLECULES, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0 Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Danti, B<br><br>Tel.(+49-89) 2399-8161 |

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| CRP-165PC | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US98/10909 | 29/05/1998 | 30/05/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>G01N33/50 | | |
| Applicant<br>CREATIVE BIOMOLECULES, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 17/12/1998 | 26.08.99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0 Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br>Montron , M<br>Telephone No. (+49-89) 2399 8711 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/10909

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-65 as originally filed

**Claims, No.:**

1-122 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-56,76-103.

because:

☒ the said international application, or the said claims Nos. 1-56,76-103 with respect to I.A. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-122 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-122 |
| Industrial applicability (IA) | Yes: | Claims | 57-75, 104-122 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see s parat sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

Item III:

Claims 1 to 56 and 76 to 103 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(i) PCT).

Item V:

1. WO-A-9403200 (document D1) discloses morphogen induced nerve regeneration and repair of damaged neurons, neural pathways and retina (see abstract and page 9, line 8; page 12, l. 13). In addition, compositions are disclosed consisting of biodegradable carriers which are locally or systemically administered, including orally, intravenously or parenterally (see page 10, l. 18 and page 13, l. 14; page 14, l. 33; page 17, l. 31). The morphogens are either administered alone or with compounds which enhance the solubility of the proteins or analogs (page 18, l. 5, page 20, l. 9). The following examples of morphogens are given: OP-1, OP-2, GDF-1, DPP, Vgl, Vgr-1, 60A and different BMPs (see page 18, line 23 to page 23, line 6). The biological functions of said morphogens were defined as follows: stimulate proliferation or differentiation of progenitor or differentiated cells, support growth and maintenance of differentiated cells (see page 27, l. 4). In addition, generic sequences of said morphogens are disclosed (see page 27, l. 26 to page 31, l. 37) and the C-terminal 96 to 102 amino acids of said proteins which have at least 70% homology to OP-1 (page 39, l.19). Thus, D1 is considered to be detrimental to the novelty of the subject-matter of claims 1 to 75.

   WO-A-9403600 (document D2) discloses soluble complexes of morphogenic proteins and compositions thereof (see abstract and page 1, l. 6). The morphogens of D2 are able to induce endochondral bone formation and are either locally or systemically administered (see page 1, line 21 to 25). In addition, a diagnostic method is disclosed for monitoring the concentration of said morphogens (page 3, l. 13). OP-1 from human or mouse origin and analogs thereof are disclosed as examples (page 5, l. 13). The morphogens could be used for the treatment of damages of bones, dentin, periodontal, liver, heart, nerve tissue and kidney or pancreas tissue (see page 9, l. 7 to 28 and page 51, l. 15). The composition is administered either orally, parenterally

or systemically (page 51, l. 27). The OP-1 is provided in an aqueous solution or together with a biodegradable matrix (page 52, l. 4 to page 53, l. 1). The doses administered vary from 10 ng/kg to 1 g/kg up to 0.1 µg/kg to 100 mg/kg (see page 57, l. 20). Consequently, D2 is considered to be detrimental to the novelty of the subject-matter of claims 29 to 122.

WO-A-9630038 (document D3) discloses peptide growth factors or analogs or fragments thereof having epidermal inducing activity which could be used as a pharmaceutical composition for wound healing, skin culture or the treatment of certain neural tumours (see abstract and page 27, line 30 to page 28, line 5 and page 33, line 4). BMP-4 is disclosed as an example (see page 10, l. 24). Thus, D3 is considered to be detrimental to the novelty of the subject-matter of claims 29 to 75.

US-A-5169837 (document D4) discloses purified novel water-soluble osteogenic factors for the induction of bone growth and pharmaceutical compositions thereof (see abstract, col. 3, line 22; col. 7, l. 1 to col. 8, l. 31). Moreover, bioassays for evaluating the morphogenic activity of said proteins or for the evaluation of a protein-dose dependent relationship are disclosed (col. 10, l. 22 and fig. 2). Thus, D4 is considered to be detrimental to the novelty of the subject-matter of claims 1 to 5, 8 to 12, 15, 20 to 22, 76 to 87, 90, 95 to 97, 104 to 109, 111 and 114 to 116.

EP-A-0714665 (document D5) discloses osteogenic proteins and a device for the induction of bone growth (abstract). OP-1 and CBMP IIa, CBMP IIb and CBMP III as morphogens are mentioned (page 4). A composition of said proteins is used to correct skeletal or dental abnormalities, to induce endochondral bone formation and cartilage repair (see page 5, line 27 to 49). Moreover, an in vivo method is disclosed for evaluating bone inducing activity of said proteins (page 25, line 20). Thus, D5 is considered to be detrimental to the novelty of the subject-matter of claims 1, 3, 5, 7 to 11, 15, 23 to 26, 28, 29, 35 to 40, 43, 49 to 54, 56, 57, 59, 62, 64, 68, 70 to 73, 75, 76, 80 to 87, 90, 96 to 101, 103, 104, 106, 109, 111, 115 to 120 and 122.

EP-A-0723031 (document D6) discloses biosynthetic water-soluble osteogenic proteins and devices containing them. Moreover, a pharmaceutical composition and methods for the induction of endochondral bone growth, treatment of dental abnormalities and cartilage repair in mammals are disclosed (see abstract and claims

10 and 18). Several "natural" and "synthetic" morphogens are mentioned (see page 6 to page 7, line 48). In addition, an in vivo rat bioassay is disclosed for the evaluation of the morphogenic activity of proteins (page 18, l. 6). The concentration of the morphogen administered is 25 mg (page 18, l. 20). Consequently, D6 is considered to be detrimental to the novelty of the subject-matter of claims 1, 5, 7 to 12, 15, 21 to 26, 28, 29, 35 to 40, 43, 49 to 54, 56 to 58, 61, 62, 64, 65, 68 to 73, 75, 76, 80 to 87, 90, 96 to 101, 103, 104, 106, 108, 109, 111, 112, 115 to 120 and 122.

WO-A-9305172 (document D7) discloses a screening method for compounds which can modulate the level of morphogenic proteins in a mammalian system (see abstract and page 4, l. 3 to page 5, l. 7). The assay disclosed is identical to the one used in the present application in order to find and evaluate said compounds. The only difference is that it refers particularly to substances which are able to modulate the level of a known morphogen, such as OP-1.

WO-A-9514104 (document D8) discloses a further in vivo method for identifying substances capable of inducing bone formation. However, like in D7, it is not the morphogen itself which is evaluated for being morphogenic but rather a substance which either stimulates or inhibits OP-1 gene expression (see abstract; page 4, line 12 to 26 and page 19, line 7).

Consequently, the subject-matter of claims 1 to 122 of the present application is not considered to be novel over the cited prior art. Thus, said claims do not fulfil the requirements of Article 33(2) PCT.

2. For the assessment of the present claims 1 to 56 and 76 to 103 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI:

The documents WO-A-9813509 filed at the 24.09.1997, published at 02.04.1998 and claiming the priority of 24.09.1996, US-A-5641743 filed at the 26.05.1995, published at 24.06.1997 and claiming the priority of 26.05.1995 and WO-A-9732033 filed at the 28.02.1997, published at 04.09.1997 and claiming the priority of 28.02.1996 could be relevant to the subject-matter of the present application if the priority of the claims is not valid. In addition, said documents could be relevant for the question of novelty under Article 54(3) and (4) EPC if the application enters the regional phase in Europe.

Item VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3, D4, D5 and D6 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

1. The terms:
"aged" used in claims 8, 22, 50, 97
"reduced capacity" used in claims 9, 11, 37, 39, 84, 86
"obese" used in claims 22, 50, 97
"hypertensive" used in claims 22
"steroidal drug user" used in claims 21, 49, 96
have a relative meaning and are thus vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

2. The term "defines a volume" used in claim 81 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

3. The subject-matter of claim 24 is already covered by the subject-matter of claim 23 rendering the scope of protection of said claim unclear, contrary to the requirements of Article 6 PCT. The same applies to the subject-matter of claims 52 and 51, 71 and 70, 99 and 98 and 118 and 117.

4. The subject-matter of claims 1, 3, 29, 31, 32, 57, 76, 78, 79 and 104 is vague and unclear since they are formulated in a "result to be achieved" manner without disclosing any substantial technical features. This renders the definition of the subject-matter of said claims and their scope unclear (Article 6 PCT).

5. There is no experimental support given in the application as filed that every "morphogen" sharing at least 70 % homology within the C-terminal 102-106 amino acids of the human OP1 protein does indeed induce tissue formation, tissue repair or enhances callus formation as claimed in claims 25, 53, 72, 100 or 119, contrary to the requirements of Article 6 PCT. Furthermore, the subject-matter of said claims is not disclosed by the description in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 5 PCT).

6. The same applies to the generic sequences as referred to in claims 28, 56, 75, 103 and 122 being disclosed on page 25, line 20 et seq. of the description in an uncountable number of different amino acid combinations. No biologic function has been disclosed for said alleged morphogenic proteins and due to an endless number of all possible combinations it is as well doubted that every combination has morphogenic properties. Moreover, for the skilled person it is not possible to find the potentially effective combinations in the claimed range of "generic" morphogenic proteins. Thus, the subject-matter of said claims is not disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 5 PCT).

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| CRP-165PC | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US 98/ 10909 | 29/05/1998 | 30/05/1997 |
| Applicant | | |
| CREATIVE BIOMOLECULES, INC. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   METHODS FOR EVALUATING TISSUE MORPHOGENESIS AND ACTIVITY

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

# I RNATIONAL SEARCH REPORT

International Application No
PCT/US 98/10909

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/50 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N A61K C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | EP 0 723 013 A (STRYKER CORP) 24 July 1996<br>see claims 10,18<br>see page 4, line 20 - line 22<br>see page 8, line 14 - line 19<br>see page 24, line 49 - line 57<br>--- | 76-122 |
| X | EP 0 714 665 A (STRYKER CORP) 5 June 1996<br>see claim 9<br>see page 5, line 28 - line 49<br>see page 24, line 23 - page 27, line 54<br>--- | 76-122 |
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 October 1998 | 28/10/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Routledge, B |

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Form PCT/ISA/210 (second sheet) (July 1992)

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| Y | see claims<br>see page 8, line 25 - page 10, line 13<br>see page 27, line 30 - page 28, line 5<br>see page 33, line 4 - page 35, line 24 | 1-28 |
| X | WO 95 14104 A (CHILDRENS MEDICAL CENTER ;HARRIS H WILLIAM (US); PAREDES ANA (US);)<br>26 May 1995 | 29-122 |
| Y | see claims<br>see page 4, line 12 - page 5, line 5<br>see page 12, line 32 - page 13, line 30<br>see page 19, line 7 - line 18<br>see page 20, line 29 - page 21, line 17<br>see page 25, line 4 - line 16 | 1-28 |
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